



ATTORNEYS AT LAW

Robert Greene Sterne  
Edward J. Kessler  
Jorge A. Goldstein  
David K.S. Cornwell  
Robert W. Esmond  
Tracy-Gen G. Durkin  
Michele A. Cimbala  
Michael B. Ray  
Robert E. Sokohl  
Eric K. Steffe  
Michael Q. Lee  
Steven R. Ludwig  
John M. Covert  
Linda E. Alcorn  
Robert C. Milionig  
Lawrence B. Bugaisky  
Donald J. Featherstone  
Michael V. Messinger

Judith U. Kim  
Timothy J. Shea, Jr.  
Patrick E. Garrett  
Jeffrey T. Helvey  
Heidi L. Kraus  
Edward W. Yee  
Albert L. Ferro\*  
Donald R. Banowitz  
Peter A. Jackman  
Molly A. McCall  
Teresa U. Medler  
Jeffrey S. Weaver  
Kendrick P. Patterson  
Vincent L. Capuano  
Albert J. Fasulo II\*  
Eldora Ellison Floyd  
Thomas C. Fiala  
Brian J. Del Buono

Virgil Lee Beaston\*  
Kimberly N. Reddick  
Theodore A. Wood  
Elizabeth J. Haanes  
Bruce E. Chalker  
Joseph S. Ostroff  
Frank R. Cottingham  
Christine M. Lhulier  
Rae Lynn Prengaman  
Jane Sherbenovich\*  
Lawrence J. Carroll\*  
George S. Bardmessner  
Daniel A. Klein\*  
Rodney G. Maze  
Jason D. Eisenberg  
Michael A. Specht\*  
Andrea J. Kamage  
Tracy L. Muller\*

Jon E. Wright\*  
LuAnne M. Yuricek\*  
Registered Patent Agents\*  
Karen R. Markowicz  
Nancy J. Leith  
Ann E. Summerfield  
Helene C. Carlson  
Gaby L. Longsworth  
Matthew J. Dowd  
Aaron L. Schwartz  
Angelique G. Uy  
Boris A. Matvenko  
Mary B. Tung  
Katrina Y. Pei  
Bryan L. Skelton  
Robert A. Schwartzman  
John J. Figueira

Timothy A. Doyle  
Jennifer R. Mahalingappa  
Teresa A. Coletta  
Jeffrey S. Lundgren  
Victoria S. Rutherford  
W. Brian Edge  
Senior Counsel  
Samuel L. Fox  
Kenneth C. Bass III  
Lisa A. Dunner

\*Admitted only in Maryland  
\*Admitted only in Virginia  
\*Admitted only in Texas  
\*Practice Limited to  
Federal Agencies

February 14, 2003

**WRITER'S DIRECT NUMBER:**  
(202) 772-8673

**INTERNET ADDRESS:**  
JCOVERT@SKGF.COM

***Via Facsimile***

Commissioner for Patents  
Washington, D.C. 20231

***Confirmation Copy Via Hand Carry***  
***Group Art Unit 1626***  
***Examiner G. Shameem***

Re: U.S. Utility Patent Application  
Appl. No. 09/814,123; Filed: March 22, 2001  
For: **Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use  
Thereof**  
Inventors: HOGENKAMP *et al.*  
Our Ref: 1861.1270001/JMC/THN

Sir:

Transmitted herewith for appropriate action are the following documents:

1. Supplemental Amendment and Reply; and
2. One (1) return postcard.

It is respectfully requested that the attached postcard be stamped with the date of filing of these documents, and that it be returned to our courier. In the event that extensions of time are necessary to prevent abandonment of this patent application, then such extensions of time are hereby petitioned.

Commissioner for Patents  
February 14, 2003  
Page 2

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 19-0036.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



John M. Covert

Attorney for Applicants  
Registration No. 38,759

Enclosures

SKGF\_DC1:102710.1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

HOGENKAMP *et al.*

Appl. No. 09/814,123

Filed: March 22, 2001

For: **Aryl Substituted Pyrazoles,  
Triazoles and Tetrazoles, and the Use  
Thereof**

Confirmation No. 2060

Art Unit: 1626

Examiner: Shameem, G.

Atty. Docket: 1861.1270001/JMC/THN

**Supplemental Amendment and Reply**

Commissioner for Patents  
Washington, D.C. 20231

Sir:

In reply to the Examiner's request during a telephone conference of February 4, 2003, Applicants submit the following Amendment and Remarks. This Amendment is provided in the following format:

- (A) A clean version of each replacement paragraph/section/claim along with clear instructions for entry;
- (B) Starting on a separate page, appropriate remarks and arguments. 37 C.F.R. § 1.111 and MPEP 714; and
- (C) Starting on a separate page, a marked-up version entitled: "Version with markings to show changes made."

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees

for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 19-0036.

***Amendment***

***In the Claims:***

Please substitute the following claim 3 for the pending claim 3:

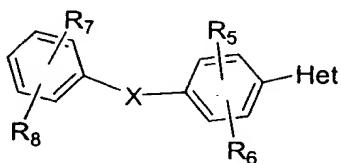
3. (Once Amended) A compound of claim 2, wherein R<sub>10</sub> is selected from the group consisting of C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, OR<sub>10</sub>, amino, C<sub>1-6</sub> alkylamino, di(C<sub>1-6</sub>)alkylamino, C<sub>2-6</sub> alkenylamino, and di(C<sub>1-6</sub>)alkylamino(C<sub>2-6</sub>)alkenyl.

Please substitute the following claim 15 for the pending claim 15:

15. (Three Times Amended) A compound of claim 1, wherein:  
R<sub>1</sub> is C(O)R<sub>10</sub>, CH<sub>2</sub>C(O)R<sub>10</sub>, or SO<sub>2</sub>R<sub>10</sub>;  
X is O or S;  
R<sub>10</sub> is amino, optionally substituted C<sub>1-C<sub>6</sub></sub> alkyl, or a heterocycle;  
R<sub>2</sub>, and R<sub>3</sub> are independently hydrogen, C<sub>1-C<sub>6</sub></sub> alkyl, C<sub>1-C<sub>6</sub></sub> alkylthio or C<sub>1-C<sub>6</sub></sub> alkylsulfinyl,  
R<sub>5</sub> and R<sub>6</sub> are as defined in claim 1, and  
R<sub>7</sub> and R<sub>8</sub> are independently selected from the group consisting of hydrogen, halo, halo(C<sub>1-C<sub>6</sub></sub>)alkyl, C<sub>1-C<sub>6</sub></sub> alkyl, hydroxy(C<sub>1-C<sub>6</sub></sub>)alkyl, amino(C<sub>1-C<sub>6</sub></sub>)alkyl, carboxy(C<sub>1-C<sub>6</sub></sub>)alkyl, alkoxy(C<sub>1-C<sub>6</sub></sub>)alkyl, nitro, amino, C<sub>1-C<sub>6</sub></sub> acylamino, amide, hydroxy, thiol, C<sub>1-C<sub>6</sub></sub> acyloxy, C<sub>1-C<sub>6</sub></sub> alkoxy, carboxy, carbonylamido and C<sub>1-C<sub>6</sub></sub> alkylthiol.

Please substitute the following claim 16 for the pending claim 16:

16. (Three Times Amended) A compound of Formula *I*:

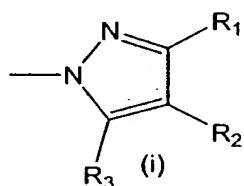


*I*

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is



R1 is C(O)R10, CH2C(O)R10, or SO2R10 wherein R10 is amino, all of which are optionally substituted;

R2 and R3 are independently hydrogen, C1-C6 alkyl, C1-C6 alkylthio or C1-C6 alkylsulfinyl; and

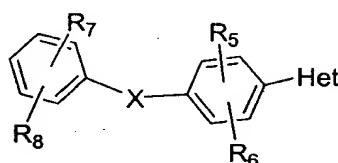
R5, R6, R7 and R8 are independently selected from the group consisting of hydrogen, halo, halo(C1-C6)alkyl, C1-C6 alkyl, hydroxy(C1-C6)alkyl, amino(C1-C6)alkyl, carboxy(C1-C6)alkyl, alkoxy(C1-C6)alkyl, nitro, amino, C1-C6 acylamino, amide, hydroxy, thiol, C1-C6 acyloxy, C1-C6 alkoxy, carboxy, carbonylamido and C1-C6 alkylthiol.

Please substitute the following claim 17 for the pending claim 17:

17. (Once Amended) A pharmaceutical composition, comprising the compound of any one of claims 1, 16, 22, or 25 and a pharmaceutically acceptable carrier.

Please substitute the following claim 22 for the pending claim 22:

22. (Three Times Amended) A compound of Formula *I*:

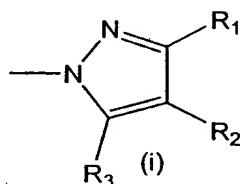


*I*

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is



R<sub>1</sub> is C(O)R<sub>10</sub>, wherein R<sub>10</sub> is amino, all of which are optionally substituted;

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio or C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; and

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently selected from the group consisting of hydrogen, halo, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, amino, C<sub>1</sub>-C<sub>6</sub> acylamino, amide, hydroxy, thiol, C<sub>1</sub>-C<sub>6</sub> acyloxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy, carbonylamido and C<sub>1</sub>-C<sub>6</sub> alkylthiol.

Please add the following new claims 28-31:

28. (New) A method of treating a disorder responsive to the blockade of sodium channels in a mammal suffering therefrom, comprising administering to a mammal in need of such treatment an effective amount of the compound as claimed in any one of claims 1, 16, 22, or 25.

29. (New) A method for treating or ameliorating neuronal loss following global and focal ischemia; treating or ameliorating neurodegenerative conditions; treating or ameliorating pain or tinnitus; treating or ameliorating manic depression; providing local anesthesia; treating arrhythmias, or treating convulsions, comprising administering to a mammal in need of such treatment an effective amount of the compound as claimed in any one of claims 1, 16, 22, or 25.

30. (New) The method of claim 29, wherein the method is for treating or ameliorating pain and said pain is one of neuropathic pain, surgical pain or chronic pain.

31. (New) A method of alleviating seizure activity in an animal subject, comprising administering to a mammal in need of such treatment an effective amount of a compound of any one of claims 1, 16, 22, or 25.

**Remarks**

Reconsideration of this Application is respectfully requested.

The Examiner requested on February 4, 2003, that claims 3, 15, 16, and 22 be amended by canceling the reference to "N-morpholinyl", "N-pyrrolidinyl", and "N-piperazinyl" as definitions for R<sub>10</sub>, and that copies of the references listed on Form PTO-1449 resubmitted on May 9, 2002, be resubmitted.

During a telephone conference on February 5, 2003, the Examiner agreed that claim 15 can be amended by canceling the phrase "selected from the group consisting of N-morpholinyl, N-pyrrolidinyl, and N-piperazinyl" from the definitions of R<sub>10</sub>, leaving the term "heterocycle" as a definition for R<sub>10</sub>.

During a telephone conference of February 13, 2003, it was brought to the Examiner's attention that Applicants wish to amend claim 17, directed to pharmaceutical compositions, to be dependent also on independent claims 22 and 25 in addition to claims 1 and 16. Furthermore, the Examiner indicated that he is willing to rejoin and consider the method claims 18-21, canceled in the previous Amendment of November 27, 2002, as long as they are specifically adapted to the allowable compounds and they are amended in such a way that no § 112, paragraph issues rise. Specifically, the Examiner requested the deletion of the term "preventing" from all the method claims.

Applicants resubmitted the references originally submitted along with Form PTO-1449 accompanying Applicants' Information Disclosure Statement, filed December 13, 2001 and resubmitted by facsimile on May 9, 2002, on February 13,

2003 via hand carry. Applicants respectfully request the Examiner to provide a copy of the initialed and signed PTO-1449 forms.

Claims 3, 15, 16, 17, and 22 are sought to be amended, and new claims 28-31 are sought to be added. Claims 3, 15, 16, and 22 have been amended by amending the definitions for R<sub>10</sub> as requested by the Examiner. Applicants submit that no new matter has been introduced by this amendment since deletion of individual members of a Markush expression does not constitute new matter. *See In re Johnson and Farnham*, 558 F.2d 1008, 1019, 194 U.S.P.Q. 187, 196 (CCPA 1977). Claim 17 has been amended by amending the dependencies. Specifically, claim 17 has been amended to be dependent on all independent compound claims 1, 16, 22, and 25. Support for this amendment can be found in the original specification and claims as filed.

New claims 28-31 find support in the original claims 18-21. New claims 28-31 are specifically adapted to the allowable compounds. Further, none of claims 28-31 include the term "preventing."

These changes are believed to introduce no new matter, and their entry is respectfully requested. Upon entry of the foregoing amendment, claims 1-10, 15-17 and 22-31 are pending in the application, with claims 1, 16, 22 and 25 being the independent claims.

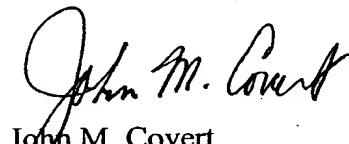
***Conclusion***

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding issues raised by the Examiner and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Supplemental Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

  
John M. Covert  
Attorney for Applicants  
Registration No. 38,759

Date: Feb. 14, 2003

1100 New York Avenue, N.W.  
Suite 600  
Washington, D.C. 20005-3934  
(202) 371-2600

**Version with markings to show changes made**

New claims 28-31 have been added.

Claims 3, 15, 16, 17, and 22 have been amended as follows:

3. (Once Amended) A compound of claim 2, wherein  $R_{10}$  is selected from the group consisting of  $C_{1-6}$  alkyl,  $C_{2-6}$  alkenyl,  $OR_{10}$ , amino,  $C_{1-6}$  alkylamino,  $di(C_{1-6})alkylamino$ ,  $C_{2-6}$  alkenylamino, and  $di(C_{1-6})alkylamino(C_{2-6})alkenyl$ ,  $N$ -morpholinyl,  $N$ -pyrrolidinyl, and  $N$ -piperazinyl].

15. (Three Times Amended) A compound of claim 1, wherein:

$R_1$  is  $C(O)R_{10}$ ,  $CH_2C(O)R_{10}$ , or  $SO_2R_{10}$ ;

$X$  is O or S;

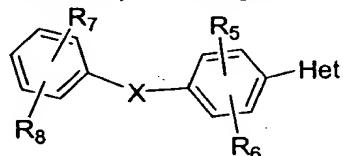
$R_{10}$  is amino, optionally substituted  $C_{1-C_6}$  alkyl, or a heterocycle [selected from the group consisting of  $N$ -morpholinyl,  $N$ -pyrrolidinyl and  $N$ -piperazinyl];

$R_2$ , and  $R_3$  are independently hydrogen,  $C_{1-C_6}$  alkyl,  $C_{1-C_6}$  alkylthio or  $C_{1-C_6}$  alkylsulfinyl,

$R_5$  and  $R_6$  are as defined in claim 1, and

$R_7$  and  $R_8$  are independently selected from the group consisting of hydrogen, halo, halo( $C_{1-C_6}$ )alkyl,  $C_{1-C_6}$  alkyl, hydroxy( $C_{1-C_6}$ )alkyl, amino( $C_{1-C_6}$ )alkyl, carboxy( $C_{1-C_6}$ )alkyl, alkoxy( $C_{1-C_6}$ )alkyl, nitro, amino,  $C_{1-C_6}$  acylamino, amide, hydroxy, thiol,  $C_{1-C_6}$  acyloxy,  $C_{1-C_6}$  alkoxy, carboxy, carbonylamido and  $C_{1-C_6}$  alkylthiol.

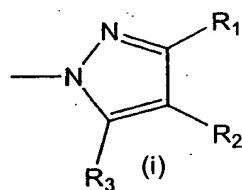
16. (Three Times Amended) A compound of Formula I:



or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

$X$  is O or S;

Het is



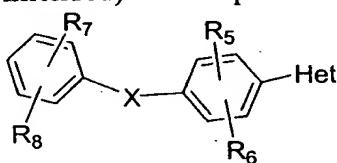
R<sub>1</sub> is C(O)R<sub>10</sub>, CH<sub>2</sub>C(O)R<sub>10</sub>, or SO<sub>2</sub>R<sub>10</sub> wherein R<sub>10</sub> is amino[,] or alkyl, [N-morpholinyl, N-pyrrolidinyl or N-piperazinyl], all of which are optionally substituted;

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio or C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; and

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently selected from the group consisting of hydrogen, halo, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, amino, C<sub>1</sub>-C<sub>6</sub> acylamino, amide, hydroxy, thiol, C<sub>1</sub>-C<sub>6</sub> acyloxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy, carbonylamido and C<sub>1</sub>-C<sub>6</sub> alkylthiol.

17. (Once Amended) A pharmaceutical composition, comprising the compound of any one of claims [claim] 1, [or] 16, 22, or 25 and a pharmaceutically acceptable carrier.

22. (Three Times Amended) A compound of Formula I:

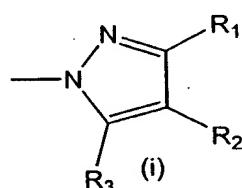


I

or a pharmaceutically acceptable salt, prodrug or solvate thereof, wherein

X is O or S;

Het is



R<sub>1</sub> is C(O)R<sub>10</sub>, wherein R<sub>10</sub> is amino[, N-morpholinyl, N-pyrrolidinyl or N-piperazinyl, all of which are optionally substituted];

R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, C<sub>1</sub>-C<sub>6</sub> alkylthio or C<sub>1</sub>-C<sub>6</sub> alkylsulfinyl; and

R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> are independently selected from the group consisting of hydrogen, halo, halo(C<sub>1</sub>-C<sub>6</sub>)alkyl, C<sub>1</sub>-C<sub>6</sub> alkyl, hydroxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, amino(C<sub>1</sub>-C<sub>6</sub>)alkyl, carboxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, alkoxy(C<sub>1</sub>-C<sub>6</sub>)alkyl, nitro, amino, C<sub>1</sub>-C<sub>6</sub> acylamino, amide, hydroxy, thiol, C<sub>1</sub>-C<sub>6</sub> acyloxy, C<sub>1</sub>-C<sub>6</sub> alkoxy, carboxy, carbonylamido and C<sub>1</sub>-C<sub>6</sub> alkylthiol.

**Applicants:** Hogenkamp *et al.*

**Application No.:** 09/814,123

**Filed:** March 22, 2001

**For:** Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof

**Due Date:** None

**Art Unit:** 1626

**Examiner:** Shameem, G.

**Docket:** 1861.1270001

**Atty:** JMC/THN

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. Supplemental Amendment and Reply; and
3. One (1) return postcard.

**Applicants:** Hogenkamp *et al.*

**Application No.:** 09/814,123

**Filed:** March 22, 2001

**For:** Aryl Substituted Pyrazoles, Triazoles and Tetrazoles, and the Use Thereof

**Due Date:** None

**Art Unit:** 1626

**Examiner:** Shameem, G.

**Docket:** 1861.1270001

**Atty:** JMC/THN

When receipt stamp is placed hereon, the USPTO acknowledges receipt of the following documents:

1. SKGF Cover Letter;
2. Supplemental Amendment and Reply; and
3. One (1) return postcard.

RECEIVED  
TECH CENTER 1600/2300  
03 FEB 14 PM 3:27

*Via Hand Carry  
Group Art Unit 1626  
Examiner G. Shameem*

February 14, 2003

SKGF\_DCI:102711.1

Please Date Stamp And Return To Our Courier